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TITLE: **Targeting Phosphatidylserine for Radioimmunotherapy of
Breast Cancer Brain Metastasis**

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13. Abstract Brain metastasis occurs in ~30% of metastatic breast cancer patients. The prognosis is extremely poor, with a median survival of 4-6 months even with aggressive treatment. Thus, there is an urgent need to develop new treatments that target brain metastases. Radioimmunotherapy (RIT) is a targeted therapy that uses radiolabeled antibodies against tumor-specific antigens to treat lymphoma patients. However, success of RIT in the therapy of solid tumors has generally been limited due to heterogeneous tumor expression of the target antigens and cross-reactivity with normal cells. In preliminary studies, we have demonstrated that phosphatidylserine (PS) is exposed exclusively on tumor vascular endothelium of brain metastases in mouse models. A novel PS-targeting antibody, PGN635, a fully human monoclonal antibody, was used to target exposed PS in the brain metastases. Our data show that PGN635 binds specifically to tumor vascular endothelial cells in multi-focal brain metastases throughout the whole mouse brain. Vascular endothelium in normal brain tissues is negative. Furthermore, pretreatment with 10Gy of whole brain radiation significantly increased PGN635 binding to tumor vascular endothelial cells and tumor cells by increasing their exposure of PS. Vasculature in irradiated normal brain remained negative for exposed PS.				
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Introduction:

Brain metastasis occurs in ~20% of patients with breast cancer. The prognosis is extremely poor, with a median survival of 4-6 months no matter how aggressive treatment the patients received (1, 2). The incidence of brain metastasis seems to have increased over the past decade. Perhaps even more alarming are the growing numbers of breast cancer patients who die from complications related to brain metastasis, at a time when systemic disease is under good control (3-5). The majority of brain metastases patients exhibit multiple tumors at the time of diagnosis. Even in the event of a solitary metastasis, it is believed that the entire brain can be seeded with many radiographically invisible metastases. Due to the high incidence of multiple brain lesions and the limited leakage of most chemotherapeutics through blood brain barrier (BBB), the standard care for these patients is whole brain radiotherapy (WBRT). WBRT, however, is often associated with neurological complications that preclude sufficient doses delivered to tumor lesions (2, 6). Thus, there is an urgent need to develop new treatment regimens against the devastating disease.

Monoclonal antibody-based therapies, *i.e.*, anti-Her2 trastuzumab, are demonstrating clinical efficacy in treating primary breast cancer (7). However, inability to cross BBB limits their application for treatment of brain metastases. Radioimmunotherapy (RIT), by linking antibodies with radioisotopes, enhances tumor cytotoxicity by directly killing antibody-binding tumor cells or killing neighboring tumor cells by crossfire effect (8, 9). RIT thus offers an opportunity to selectively radiate tumor cells while sparing normal tissues. The high energy β^- emitter, Yttrium-90 (^{90}Y), a FDA approved radiotherapeutic, has been successfully used clinically to treat Non-Hodgkin's lymphomas (10, 11). However, success of RIT in the therapy of solid tumors has generally been limited due to heterogeneous tumor expression of the target antigens and cross-reactivity with normal cells.

Our preliminary studies have found that phosphatidylserine (PS) is exposed extensively on tumor vascular endothelium of brain metastases, but not blood vessels of normal brain in a mouse model of breast cancer brain metastasis (12). A novel PS-targeting, fully human antibody, PGN635, has been applied and showed a great sensitivity and specificity of binding exposed PS in these brain metastases. Furthermore, pretreatment with low dose of whole brain radiation significantly increased PGN635 binding to tumor vascular endothelial cells and tumor cells by increasing their exposure of PS. Given it's specifically for tumor vasculature and the lack of a need to cross the BBB, we propose to apply PGN635 RIT to treat brain metastasis of breast cancer in mouse models. We further hypothesize that RIT in combination with low dose WBRT will not only achieve effective treatment of brain metastases but also minimize the side effects.

Because PS is the same molecule and has the same distribution and regulation in all mammalian species, it is likely that the mouse data will extrapolate to humans. We believe that successful completion of this project will lay a foundation for clinical development of a novel treatment for breast cancer brain metastasis.

Body:

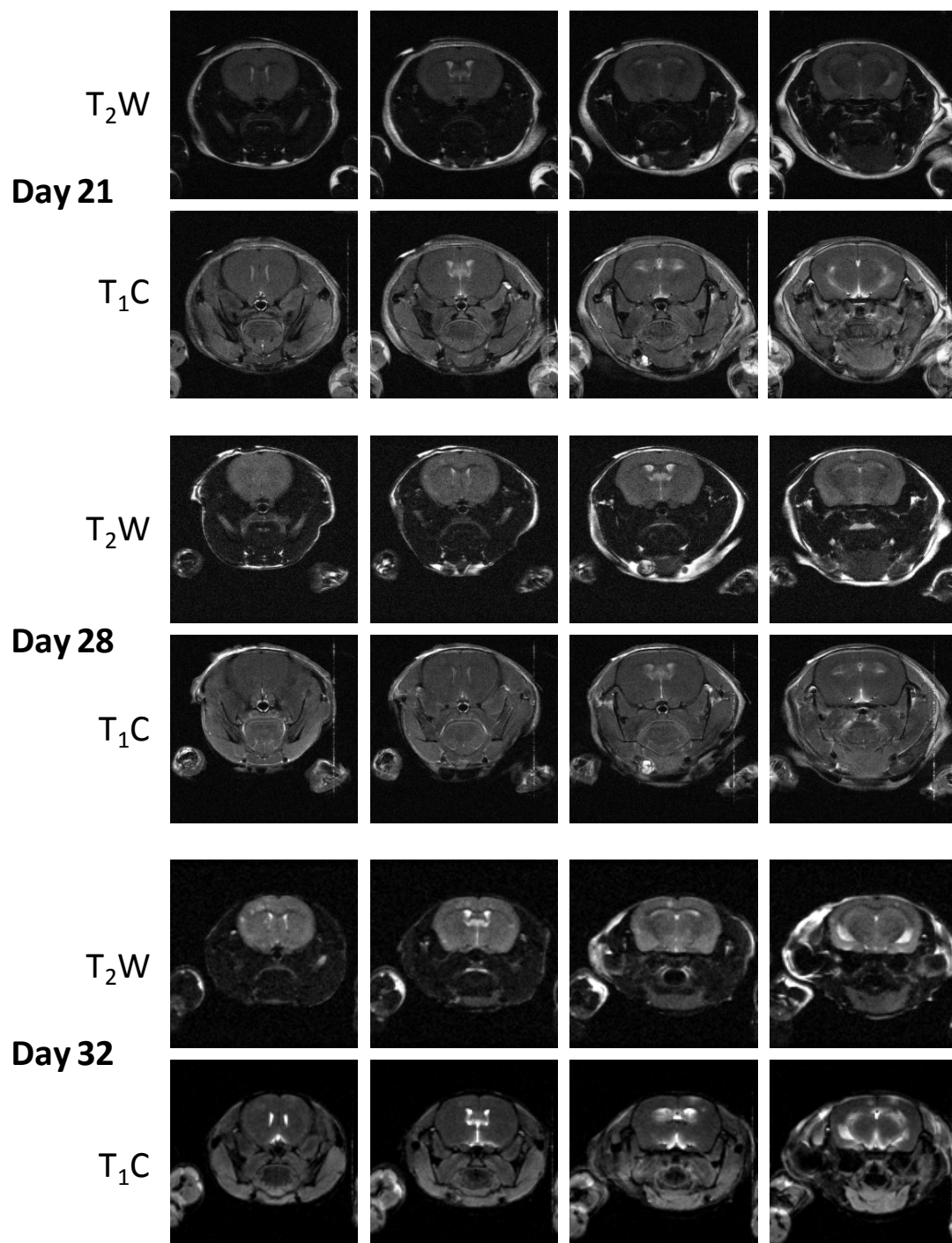
The Statement of Work in this period had two major tasks:

Task 1. To study phosphatidylserine (PS) exposure on tumor vasculature and tumor cells of breast cancer brain metastasis mouse models, and determine if exposed PS is increased by radiation.

a. Establishment of various breast cancer brain metastases mouse models:

The intracardiac model of Breast cancer brain metastasis has been successfully established by ultrasound-guided left ventricle injection of various breast cancer brain seeking cells, including MDA-MB231Br-EGFP, MCF7Br-Her2 (kindly provided by Drs. Palmieri and Steeg) and syngeneic 4T cells.

Extensive longitudinal MRI studies were conducted to non-invasively monitor the initiation and intracranial development. MRI observed multifocal brain metastases in the MDA-MB231Br (Fig. 1a) model while a solitary metastasis in the MCF7Br-Her2 model (Fig. 1b) and the 4T1 model (Fig. 1c).



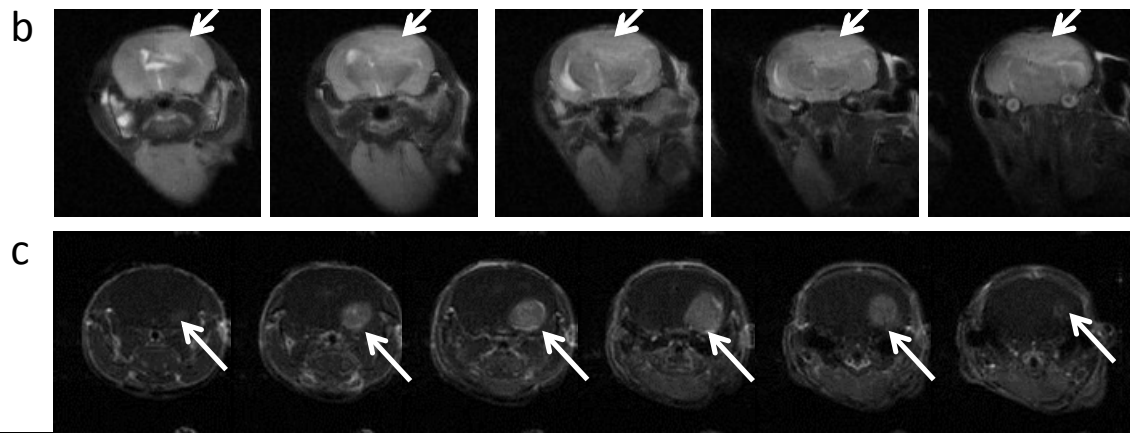
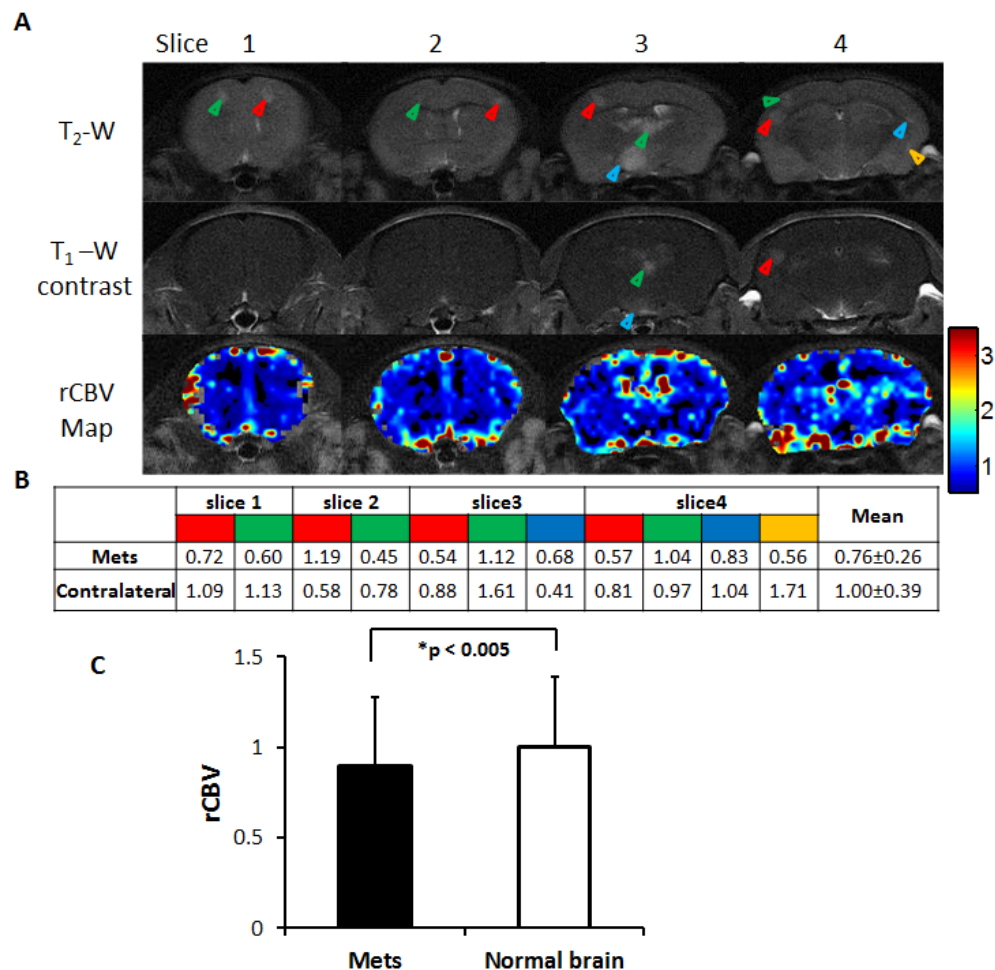


Fig. 1 MRI detection of brain metastases of mouse models. **a.** Longitudinal MRI monitoring of intracranial development of multifocal brain metastases in the MDA-MB231Br-EGFP model. **b and c.** A solitary brain metastasis was identified for the MCF7Br-Her2 and the 4T1 model, respectively.

b. MRI monitoring of intracranial growth of brain metastasis and vascularity:
Extensive MRI studies of development of intracranial metastases and their vasculature have been conducted (Fig. 2A-C). Functional MRI measurements of vascular perfusion revealed significantly lower tumor perfusion in metastases as compared to the contralateral normal brain. The observations concur well with histological study of microvessel density (MVD, Fig. 2D-F).



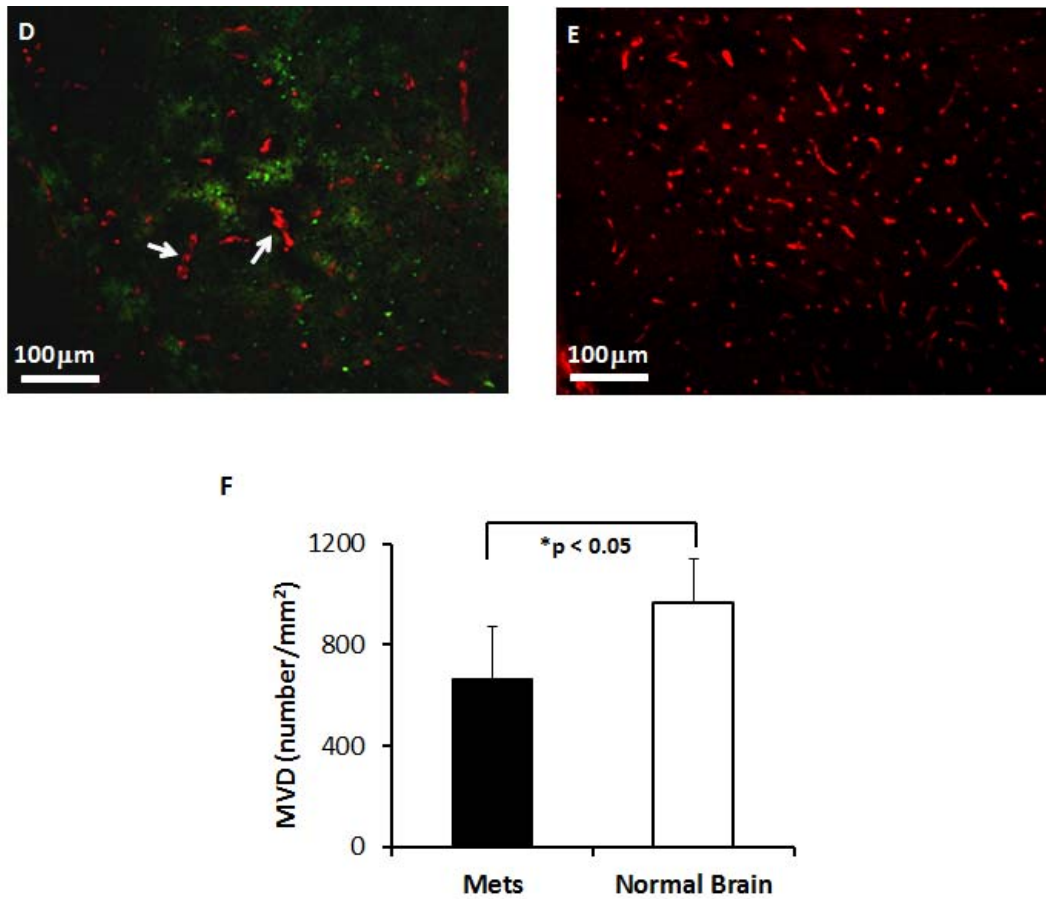


Fig. 2 MRI evaluation of tumor vascularity of brain metastases and correlating with histological studies. **A.** Four weeks after intracardiac injection of 231Br cells, T₂-weighted MRI revealed multiple high signal intensity lesions (arrowheads) on four consecutive coronal sections of a representative mouse brain. Only a few of the lesions (arrowheads) were enhanced on T₁-weighted post contrast images, one (blue arrowhead in the MRI section 3) of which showed partial enhancement, indicating intratumoral heterogeneity of BTB disruption. rCBV maps of the four sections were generated and overlaid on the T₂-weighted images. **B.** The rCBV values of the metastatic lesions and their contralateral normal brain were obtained and summarized in the table. Note the color presented in the table coincides with the color of arrowhead on each of the MR images. Most of metastatic lesions had lower rCBV values than their contralateral counterparts of normal brain. **C.** Statistical analysis of rCBV in a total of 212 lesions of 9 animals obtained from the last follow-up MRI showed significantly lower rCBV of the metastatic tumors with a mean value of 0.89 ± 0.03 (s.e.), compared to the contralateral normal brain (mean = 1.00 ± 0.03 ; $p < 0.005$). **D.** Anti-CD31 staining was performed on a brain section bearing metastases. A cortical lesion (~ 600 μ m in diameter) was depicted with green fluorescence (GFP). Microvessels (red) within the lesion appeared less dense, as compared to abundant fine vessels in the contralateral normal brain tissues (**E**). Some of the tumor vessels were irregular in shape and larger in diameter (arrow). **F.** Quantitative data of MVD showed a significantly lower MVD in brain metastases versus contralateral normal brain (mean = $669 \pm 201/\text{mm}^2$ vs. $965 \pm 177/\text{mm}^2$; $p < 0.05$).

T₁-weighted contrast enhanced MRI was applied to study BTB permeability of brain metastases. A total of 464 metastases were studied, of which 160 (34%) lesions were enhanced on T₁-weighted post contrast images, indicating a locally disrupted BTB (Figs. 3). However, enhancement in some of the metastases was only seen in partial regions of the tumor (Fig. 3), suggesting intratumoral heterogeneity of BTB disruption. Moreover, there was no significant difference in tumor size between permeable and non-permeable metastases ($p = 0.1$, Fig. 3b).

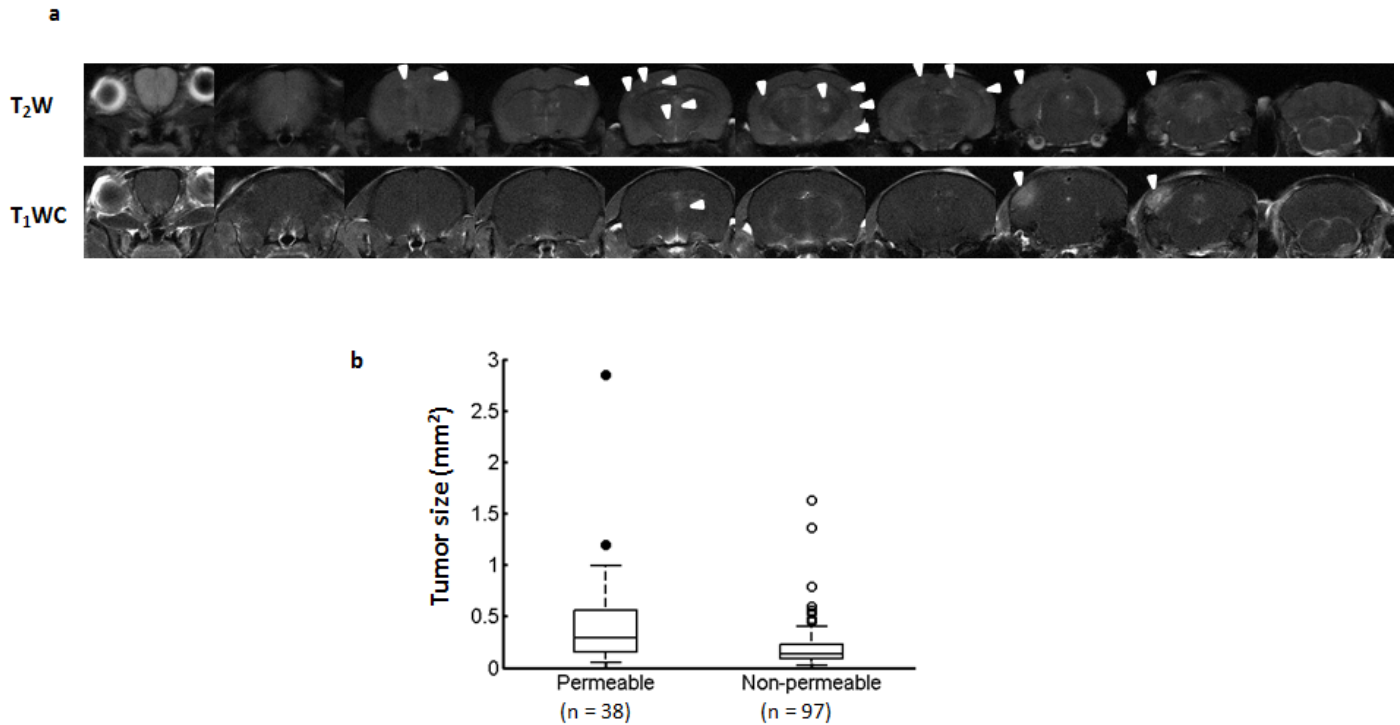


Fig. 3 MRI monitoring of intracranial distribution of brain metastases and permeability of blood-tumor-barrier. a. Ten consecutive MRI coronal sections covering the entire mouse brain were obtained from a representative mouse brain bearing 231-Br metastases. T₂-weighted images revealed hyperintense individual metastases (arrowhead) throughout the entire brain. T₁-weighted post contrast images showed enhancement only in 2 lesions (arrowhead), suggesting a disrupted BTB. **b.** A total of 128 metastases from 6 mice were separated into non-permeable and permeable metastases based on T₁-weighted post contrast images. A plot of permeability versus size indicated that larger metastases tend to be leaky. However, there was no significant difference in tumor size between permeable and non-permeable metastases ($p = 0.1$).

c. Detection and quantification of exposed PS.

PS exposure on vascular endothelium and tumor cells of brain metastases were quantified based on immunohistochemical staining of PGF635 and co-stained with vascular endothelial marker, CD31 (Fig. 4).

Individual brain metastases of MDA-MB231Br can clearly be depicted simply based on PGN635 staining (Fig. 4). Quantitative analysis of PS exposure on vascular endothelial cells of brain metastases revealed $93 \pm 5\%$ of tumor vessels had exposed PS. By contrast, the control antibody, Aurexis showed essentially no staining of blood vessels of brain metastases. The data

suggest that PS is highly specific to tumor vasculature of brain metastases (Fig. 4). Immunohistochemical studies were also conducted on investigating if tumor hypoxia induces PS exposure on vascular endothelial cells. Our data showed that there was no hypoxic regions in individual metastases by pimonidazole staining, indicating other causes than hypoxia may be related to PS exposure.

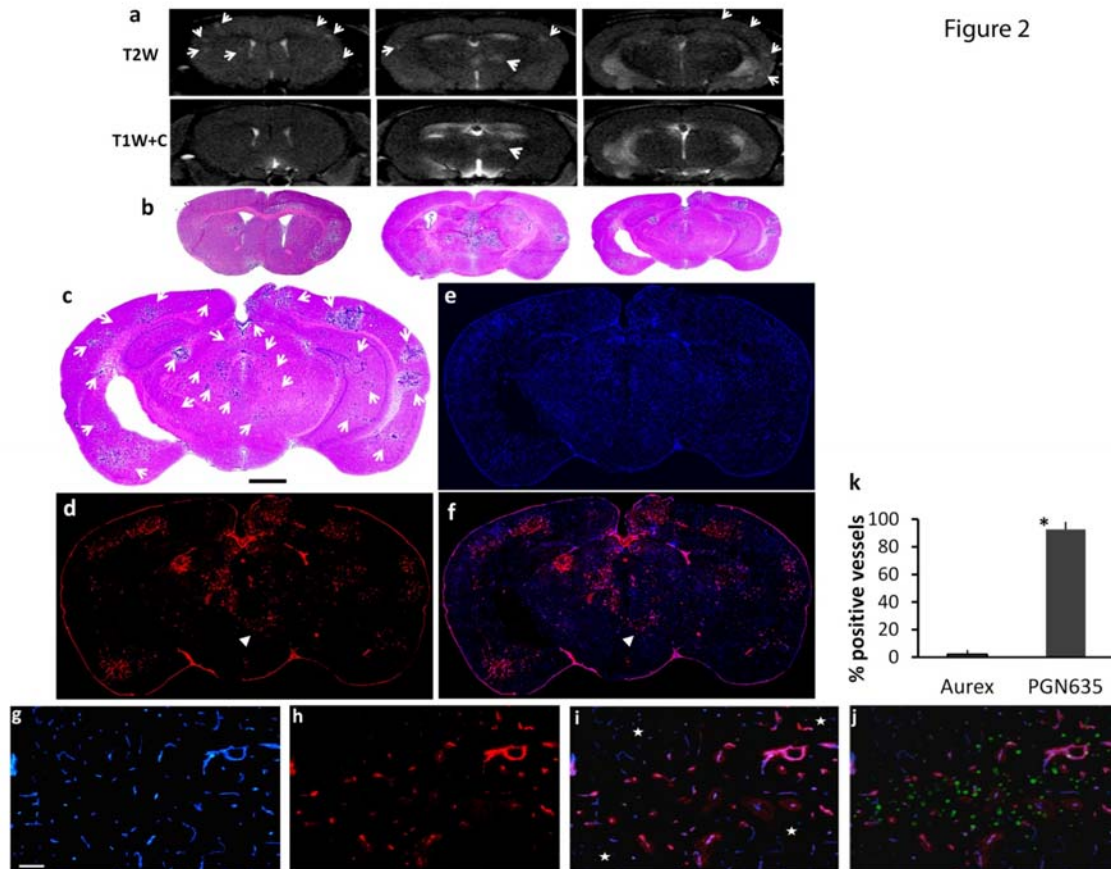


Fig. 4 Staining of PGN635 depicts individual brain metastases. **a.** H&E staining of a representative brain section bearing 231-Br metastases showed multiple lesions. **b.** Immunofluorescent staining on a consecutive section showed that PGN635 (red) localized to individual tumor lesions, even microscopic lesions. Bar=1 mm. **c-e.** A representative region containing positive PGN635 (arrow in **b**) was magnified. The merged image showed that PGN635 (red, **d**) co-localized with almost every CD31-positive tumor vessel (blue, **c**) to give a magenta color (**e**). Vessels in nearby normal brain (containing no GFP) were not stained by PGN635. **f-h.** By contrast, the control antibody, Aurexis showed essentially no staining of blood vessels of brain metastases.

d. Detection and quantification of exposed PS after whole brain radiation.

Irradiation studies with WBRT of a single dose of 10 Gy were undertaken in the brain metastasis-bearing mice. As presented in Fig. 5, a 4T1 brain metastasis was visualized on T2-weighted MRI. A 10 Gy WBRT induced significantly increased PS exposure in not only tumor vascular endothelial cells but also massive tumor cells (Fig. 5).

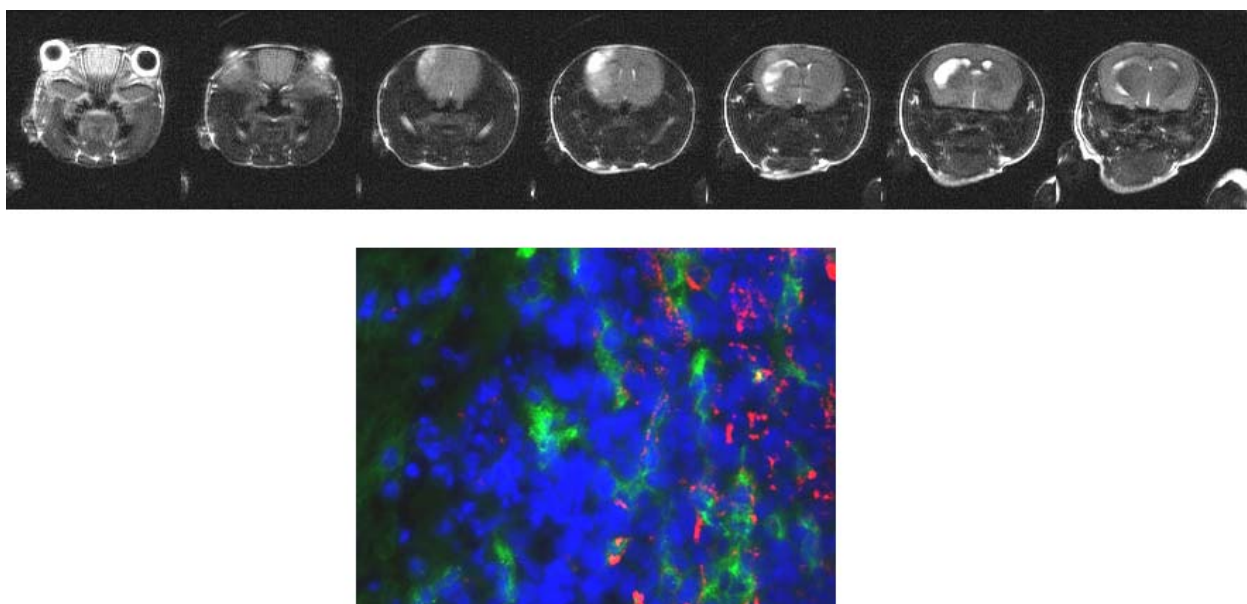


Fig. 5 Enhanced PS exposure after WBRT. Top. T2-weighted MRI clearly revealed a high-signal intensity tumor lesion. **Bottom.** After a single dose of 10 Gy WBRT, immunohistochemical staining was conducted on the tumor specimen with CD31 (green), PGN635 (red) and Dapi (blue). In addition to vascular exposed PS (orange), massive tumor cells were detected with PS exposure.

Task 2. To radiolabel the PS-targeting antibody, mch635, with β^- emitters and evaluate its biodistribution and pharmacokinetics in breast cancer brain metastasis mouse models.

- Radiolabel PGN635F(ab')₂
- Evaluate stability and binding specificity of the radio-conjugates *in vitro*.
- Develop breast cancer brain metastasis with the 4 breast cancer cell lines.
- MRI monitoring of intracranial growth of brain metastasis.
- In vivo* studies of biodistribution and dosimetry in healthy mice and in mice bearing brain metastases.

PGN635F(ab')₂ were successfully labeled with I-124 to study its specific targeting of brain metastases and biodistribution. The biodistribution data obtained for the I-124 labeled PGN635 or Aurexis at 48 h were presented in Table 1, showing that slightly higher brain radioactivity, but lower blood activity in the brain mets-bearing mice treated with I-124-PGN635 than I-124-Aurexis. Moreover, PET/CT imaging of I-124-PGN635 depicted intracranial hot spots (Fig. 6), suggesting that the radiolabeled PGN635 may serve as a specific imaging probe for sensitive detection of brain metastases in mice.

Table 1. Comparison of pharmacodistribution between I-124 labeled PGN635 and Aurexis

Organ	PGN635-1	PGN635-2	Aurexis-1	Aurexis-2
	%ID/g	%ID/g	%ID/g	%ID/g
blood	16.19	8.33	32.78	16.74
liver	8.79	7.96	3.11	1.44
spleen	4.95	7.82	3.71	2.54
muscle	1.40	7.75	0.43	10.03
skin	3.24	6.66	5.20	8.13
heart	3.90	4.91	6.59	8.74
lung	15.10	21.39	2.22	3.10
colon	3.16	2.21	1.28	0.60
intestine	3.69	3.06	2.19	0.69
brain	0.45	0.40	0.38	0.31
bladder	7.25	7.03	2.09	3.48
kidney	3.95	5.01	2.86	2.77

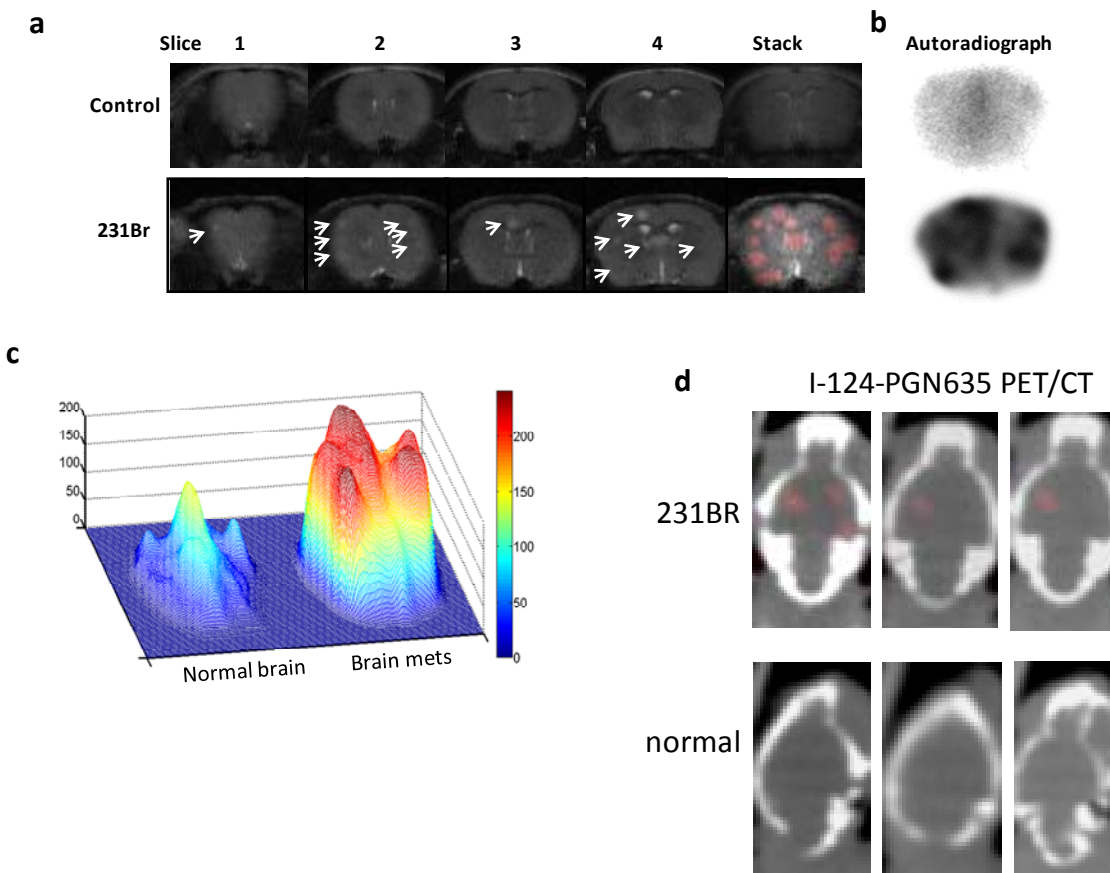


Fig. 6 Autoradiography and PET imaging of I-124/125 labeled PGN635 in targeting brain metastases. **a.** T₂-weighted MR images of 4 consecutive 1 mm thick coronal slices, covering 4mm brain tissues post bregma, were acquired from a normal control mouse brain (top) and a 231-Br brain (bottom) 40 days after intracardiac injection, respectively. Multiple tumors in the 231Br brain were identified (arrow). The stacked images were created from the 4 slices for each animal. For the tumor brain, the tumor lesions (red) from each slice were projected on the stacked image in order to correlate with autoradiography study. **b.** After MRI, each mouse was given i.v. ¹²⁵I-PGN635 F(ab')₂. Forty-eight hours later, the mice were perfused and mouse brains were dissected. Using a mouse brain matrix, 4mm thick brain tissues post bregma, correlating with the MRI, were cut from each mouse brain and laid the cutting face on the autoradiograph film. After 12 hr incubation, autoradiograph images showed multiple hot spots on the tumor brain, while clean background signal observed on the normal brain. There was also a general spatial correlation between tumor lesions on MRI and hot spots on the autoradiograph. **c.** Significantly higher uptake of ¹²⁵I-PGN635 was seen in the individual lesions, as compared to normal brain tissues (a ratio of 3.6±0.8; p < 0.05). **d.** ¹²⁴I-PGN635 F(ab')₂ (50 µg / 50 µCi) was injected into a MDA-MB231Br mouse via a tail vein. PET/CT images were acquired 24 h (not shown) and 48 h later. PET/CT merged images at 48 h showed multiple localized uptake by the mouse brain, which were highlighted on the 3 consecutive transaxial images, indicating the uptake of ¹²⁴I-PGN635 by the metastatic lesions. In contrast, there was a complete lack of uptake of ¹²⁴I-PGN635 in a normal control mouse.

Task 3. To evaluate radioimmunotherapy of breast cancer brain metastases

- Develop breast cancer brain metastasis with the 4 breast cancer cell lines.
- MRI monitoring of intracranial growth of brain metastasis.
- Perform radioimmunotherapy on established brain metastases.
- Evaluation of treatment response.
- Correlate imaging findings with histological studies of vascular damage, tumor cell and endothelial cell apoptosis or necrosis and vascular perfusion.

Task 3a and b were achieved as evidenced in Task 1 and 2 (Figs. 1-5). Radioimmunotherapy with Y-90 labeled PGN635 was performed on the brain metastasis bearing mice treated with/without WBRT. To conjugate Y-90 to PGN635, DOTA chelators were used. Significantly prolonged survival was observed in the group of WBRT + Y-90-PGN635 (p < 0.05; Fig. 7).

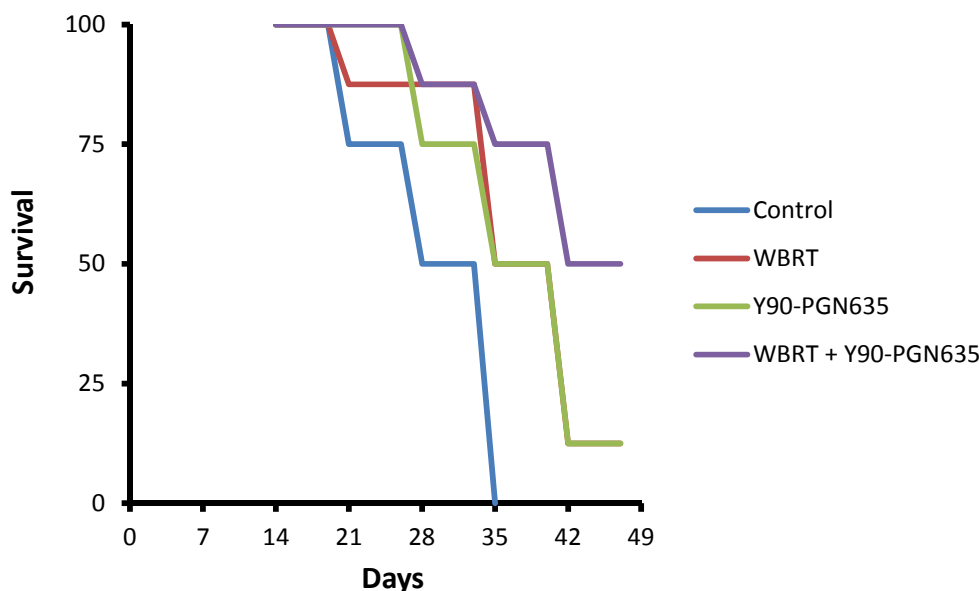


Fig. 7 **Kaplan Meier survival curve of brain metastasis bearing mice.** The combination of whole brain radiation treatment with Y90-PGN635 resulted in significantly prolonged survival compared to the untreated control group ($p < 0.05$).

Key Research Accomplishments

- Extensive imaging studies of the intracardiac model of breast cancer brain metastasis with various brain-tropic metastatic breast cancer cells including MDA-MB231Br-EGFR, MCF7Br-Her2 and syngeneic 4T1 cells.
- MRI was applied to evaluate vascular perfusion and BTB permeability of brain metastases. Our data showed significantly lower tumor perfusion in brain metastases as compared to the contralateral normal brain, and less than half of brain metastases containing disruptive blood-tumor-barrier (BTB), which correlated well with histological analyses.
- Immunohistochemical studies show PS exposure is specifically located on tumor vascular endothelial cells of brain metastases while the normal vessels surrounding the metastases lack of exposed PS, suggesting that PS can serve as a brain metastasis-specific biomarker.
- Whole brain radiation (WBRT) induced significantly more PS exposure on both tumor vascular endothelial cells and tumor cells of brain metastases.
- PS-targeting antibody, PGN635F(ab')₂ has been successfully conjugated with radioisotope, enabling in vivo PET imaging for sensitive detection of brain metastases.
- Successful conjugation of Y-90 with PGN635 via DOTA chelators.
- Experimental immunoradiotherapy with Y-90 labeled PGN635 has been conducted on the mice bearing MDA-MB231Br brain metastases.

- Prolonged survival was observed in the mice treated with Y-90-PGN635 in combined with WBRT.

Technique problem

Due to the loss of Dr. Thorpe, the Partner PI and the delay in replacement of Dr. Thorpe with Dr. Brekken, the studies, in particular, Task 2 proposed in this project were significantly delayed. Thus, a 12 month NCE was requested to fulfill the remaining studies.

Reportable Outcomes

Publications:

Peer-reviewed paper:

1. Zhou, H., Chen, M., **Zhao, D.** Longitudinal MRI evaluation of intracranial development and vascular characteristics of breast cancer brain metastases in a mouse model. *PLoS ONE*, 8(4): e62238, 2013. PMID: 23638013.
2. Zhou, H. and **Zhao, D.** Ultrasound imaging-guided intracardiac injection to develop a mouse model of breast cancer brain metastases followed by longitudinal MRI. *J. Vis. Exp.* e51146, 2014. PMID: 24637963.

Published Conference Proceedings:

1. **Zhao, D.**, Zhou, H., Stafford, J., Thorpe, P. Targeting phosphatidylserine enables the clear demarcation of brain metastases in mouse models. *Cell Symposium: Hallmarks of Cancer*, P2.028, San Francisco, CA, 2012.
2. **Zhao, D.**, Zhou, H., Stafford, J., Thorpe, P. (**Invited talk**) Imaging of tumor vascular endothelial cells in living mice. *Photonics West of SPIE*, 8596-3, San Francisco, CA, 2013.
3. **Zhao, D.**, Zhou, H., Chiguru, S., Slavine, N., Stafford, J., Thorpe, P. Phosphatidylserine targeted multimodal imaging of brain metastases in mouse models. *World Molecular Imaging Congress*, p591, Savannah, GA, 2013.
4. Zhang, L., Zhou, H., Thorpe, P., **Zhao, D.** *In vivo* MRI and optical imaging of tumor vascular endothelial cells using bimodal liposomal nanoparticles. *World Molecular Imaging Congress*, p263, Savannah, GA, 2013.

Manuscript in preparation

1. Zhou, H., Stafford, J.H., Chiguru, S. and **Zhao, D.** Targeting phosphatidylserine enables the clear demarcation of brain metastases in mouse models. Manuscript in preparation.

Employment or research opportunity:

The PhD student and research assistant, Heling Zhou, has completed her PhD dissertation and was awarded the PhD degree. Dr. Zhou is continuing her research of cancer imaging as a postdoctoral fellow in Radiology Department of UT Southwestern Medical Center.

The Postdoctoral fellow, Liang Zhang, has been recruited and been dedicating fully throughout the whole project period.

Conclusion:

During the second year of this project, we continued to perform extensive imaging and correlative histological studies to interrogate brain metastases in mouse models of various brain-tropic breast cancer cell lines. Vascular perfusion and permeability of these metastases were thoroughly assessed by functional MRI. The high sensitivity and specificity of the novel phosphatidylserine-targeting antibody, PGN635 enables individual metastases, even those micrometastases containing intact BTB to be clearly delineated. Non-invasive imaging of mice injected with PGN635 labeled with IRDye 800CW or radioisotope ^{124}I allowed clear visualization of individual brain metastases. Given its intravascular localization and the lack of a need to cross the BTB, PS appears to be an excellent biomarker for brain metastasis. Appropriate radionuclide-PGN635 conjugates may prove to be useful theranostic agents for both diagnosis and therapy for brain metastases.

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